Pfizer Inc.	PF-05190457
Mechanism of Action	Ghrelin receptor (growth hormone secretagogue 1a receptor, GHS-1aR) inverse agonist, competitive antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=246 http://www.ncbi.nlm.nih.gov/gene/2693
Overview	PF-05190457 is a potent (human K_d = 3 nM; similar across species), selective (IC_{50} > 1 uM against a broad panel of receptors, transporters, ion channels, and enzymes), and moderate on/off inverse agonist, competitive antagonist of GHS-1aR. GHS-1aRs are expressed on vagal afferents (agonism ↑ food intake), pancreatic islets (agonism ↓ insulin secretion), pituitary (agonism ↓ growth hormone secretion), hypothalamus (agonism ↑ food intake), and reward centers (agonism associated with obsessive compulsive disorders). PF-05190457 potently and in a concentration-dependent manner increases vagal afferent firing, increases glucose-dependent insulin secretion, and inhibits ghrelin-induced growth hormone release.
Safety/Tolerability	PF-05190457 was safe and generally well tolerated in humans up to 100 mg BID for 14 days which equated to an estimated 80% systemic receptor occupancy for 20 hours and 70% centrally for ~ 3 hours. Dose related increase in heart rate (up to ~10 bpm) as well as attenuation of both ghrelin-induced growth hormone secretion and postprandial glucose where seen after acute dosing. All three of these effects appeared to fully tachyphylax by day 14 of BID dosing. Nonclinical toxicology data support clinical studies up to 28 days in duration.
Additional Information	Somnolence was also seen at the 100 mg BID dose, evidence of central pharmacology, and this effect did not tachyphylax at day 14. Preliminary data suggests PF-05190457 metabolism may be catalyzed by CYP3A4 and CYP3A5.
Suitable for and Exclusions	Suitable for clinical studies up to 28 days duration in conditions/diseases of ghrelin elevation.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=PF-05190457
Publications	None yet